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MICROMACHINED STIMULATING ELECTRODES

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Summary

The goal of this project is to create and develop batch fabricated silicon technology which will enable the design of two and three dimensional implantable stimulation devices which can, under command of external electronics, create and steer electrical currents in the brain. The purpose of these devices are activation of excitable neural networks which will in turn produce sensation such as hearing or vision or produce motor activity such as the movement of limbs. It is intended that the program will provide a design space which is broad enough to accommodate a wide variety of neural prosthesis devices able to reach all parts of the central and peripheral nervous systems.

This program also includes the development of methods by which the devices are delivered safely to the site of action and the methods by which power and meaningful signals can be delivered to the devices working as neuroprostheses. Mechanisms of action and behavior of the interface between the device and the excitable tissue are explored as part of the implant system. This includes analysis of the tissue electrical response during stimulation and the histological analysis of tissue after exposure to the devices and their output over periods of time. Monitoring of device performance in tissue include estimates of device lifetime in the implant environment is also performed.

This report emphasizes a trial of one of the first active stimulating devices to be fully functional in a physiological experiment. This experiment demonstrates the functionality of the device and offers a view of the devices potential for future physiological experiments and use as a prosthetic device.

MICROMACHINED STIMULATING ELECTRODES

1. Introduction

The goal of this research is the development of active multichannel arrays of stimulating electrodes suitable for studies of neural information processing at the cellular level and for a variety of closed-loop neural prostheses. The probes should be able to enter neural tissue with minimal disturbance to the neural networks there and deliver highly-controlled (spatially and temporally) charge waveforms to the tissue on a chronic basis. The probes consist of several thin-film conductors supported on a micromachined silicon substrate and insulated from it and from the surrounding electrolyte by silicon dioxide and silicon nitride dielectric films. The stimulating sites are activated iridium, defined photolithographically using a lift-off process. Passive probes having a variety of site sizes and shank configurations have been fabricated successfully and distributed to a number of research organizations nationally for evaluation in many different research preparations. For chronic use, the biggest problem associated with these passive probes concerns their leads, which must interface the probe to the outside world. Even using silicon-substrate ribbon cables, the number of allowable interconnects is necessarily limited, and yet a great many stimulating sites are ultimately desirable in order to achieve high spatial localization of the stimulus currents.

The integration of signal processing electronics on the rear of the probe substrate (creating an "active" probe) allows the use of serial digital input data which can be demultiplexed on the probe to provide access to a large number of stimulating sites. Our goal in this area is to develop a family of active probes capable of chronic implantation in tissue. For such probes, the digital input data must be translated on the probe into per- channel current amplitudes which are then applied to the tissue through the sites. Such probes generally require five external leads, virtually independent of the number of sites used. As discussed in previous reports, we have designed a series of active probes containing CMOS signal processing electronics. Two of these probes have been completed and are designated as STIM-1A and STIM-1B. A third probe, STIM-2, is now undergoing a final iteration and is a second-generation version of our original high-end first-generation design, STIM-1. All three probes provide 8-bit resolution in digitally setting the per- channel current amplitudes. STIM-1A and -1B offer a biphasic range using ±5V supplies from 0μA to ±254μA with a resolution of 2μA, while STIM-2 has a range from 0 to ±127μA with a resolution of 1μA. STLM-2 offers the ability to select 8 of 64 electrode sites and to drive these sites independently and in parallel, while STIM-1A allows only 2 of 16 sites to be active at a time (bipolar operation). STIM-IB is a monopolar probe, which allows the user to guide an externally-provided current to any one of 16 sites as selected by the digital input address. The high-end STLM-2 contains provisions for numerous safety checks and for features such as remote impedance testing in addition to its normal operating modes. It also offers the option of being able to record from any one of the selected sites in addition to stimulation. It will be the backbone of a multi-probe three-dimensional (3D) 1024-site array (STIM-3) now in development. A new probe, STIM-2B, has now been added to this set. It offers 64-site capability with off-chip generation of the stimulus currents for four separate channels. These channels are organized in four groups so that each current can be directed to any of the 16 sites in its group, and the site can be programmed for either stimulation or recording. This probe is available in both 2D and 3D versions (as STIM-2B/3B).

2. Active Stimulating Probe Development

During the past quarter, work on the active stimulating probes has focused on the in-vitro and in-vivo validation of the STIM-2B stimulating probe design. We have tested the capability of activating the iridium (Ir) sites in parallel on an active probe. We have also tested and demonstrated the capability of the STIM-2B probe to provide selective stimulation of neurons by electronically moving the stimulus around in the probes array of sites without ever mechanically moving the probe. Also, the 3-dimensional (3D) version of this probe, referred to as STIM-3B, requires platforms and structural pieces for the completion of the 3D micro-assembly. The mask set for these 3D pieces has been completed, the masks have been made and the fabrication process has begun.

STIM-2B

In previous reports, the design of the STIM-2B probe has been described in detail. A brief overview description of the design architecture shortly. STIM-2B is a four-channel, 16-shank, 64-site probe which routes four externally generated stimulus signals to 1-of-16 sites per channel. The functionality of the STIM-2B probe has been anticipated to provide an important tool for performing some very important and interesting experiments by allowing the acute and chronic stimulation access to a relatively large volume of neural tissue without mechanically repositioning of the probe. This capability is realized by utilizing a 20b shift register to load four 4b site addresses which are decoded by a 1-of-16 nand-type decoder to connect the desired site to an analog input/output pad through a large CMOS passgate transistor thereby allowing the 'steering' of externally generated stimulus currents to the addressed site. A simple recording function has been included and is addressed by a fifth bit included with the 4b site address. This fifth bit selects between stimulation mode and recording mode by selecting either a direct path to the I/O pad from the site or a path through an amplifier for recording from the same site. Each I/O channel has its own dedicated amplifier so that the functionality of all of the channels are fairly independent of each other except for the up-front data input circuitry. A photograph of the completed etched-out STIM-2B probe circuitry is shown below in figure 1.

The fabrication of the CMOS circuitry, as discussed in previous progress reports, has been completed, the probes have been etched out and successfully bench tested. The next step was to demonstrate that this probe, STIM-2B, can be used in-vivo and that it actually performs as intended by selectively stimulating single neurons or small groups of neurons with a locally positioned site. Before this type of experiment can be performed, it is necessary to activate the Ir sites in order to increase the charge transfer capabilities between the electrical realm of the probe and the ionic realm of the tissue. Actually performing the activation of all 64 sites of the STIM-2B probe, even with the ability to independently activate all four channels in parallel, would take at least 8 hours for the 16 sites per channel. Eight hours of activation per probe is too much time, therefore, a faster method would be very helpful. Activating all of the sites of a given channel in parallel was the method of choice and is what was tested with the STIM-2B probe.

SITE ACTIVATION

The process of activating Ir to form iridium oxide on the sites of passive stimulating probes has been tested and refined previously by others that have worked in this area. A system for the activation of passive probes has been developed by a previous graduate student, but it has

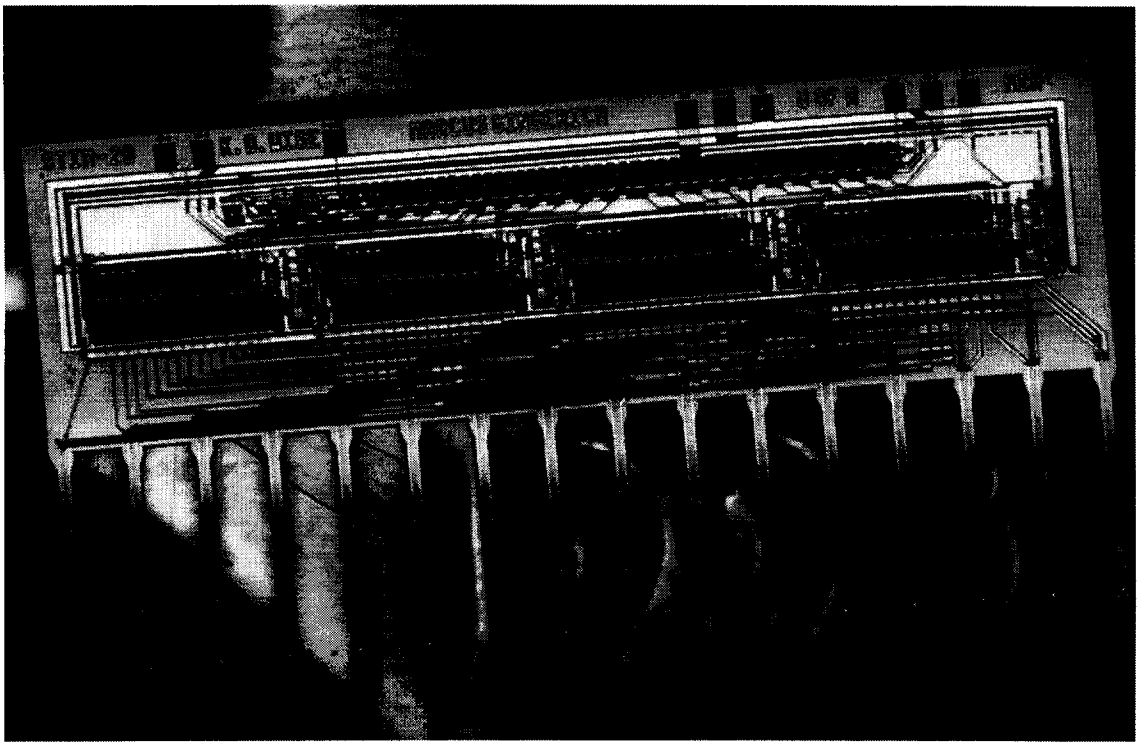

Figure 1- A photograph of the stim2B active stimulation probe

never been tested on the activation of a probe which has integrated electronics in the activation pathway. The effects of the circuitry on the activation process were unknown, though theoretically, the effects should be minimal except for the addition of some extra parasitics. Also, in general, the sites of passive probes have always been activated on a site-by-site basis not only by virtue of practicality, but also in the interest of uniformity of the level of activation from site-to-site.

The STIM-2B probe was designed with a special activation mode which connects each channel input to all 16 of its sites in parallel. The probe has a power-on-reset circuit which automatically sets the circuitry to the activation mode when power is initially applied to the probe. This is very useful in that no logic signals need to be sent to the probe, the probe need only be powered up for activation. This reduces the complexity of the system required for activation. The first clock pulse returns the probe to normal operation. The activation mode can also be initiated while the probe is in normal operating mode by pulling the clock line to -5V.

The activation of the STIM-2B probe sites in parallel was performed with all of the sites connected in parallel, the activation mode, and the variation of the activation level was observed across the sites by taking current-voltage (CV) measurements which give the charge transfer capability of the sites. A CV measurement of all 16 Channel A sites in parallel prior to activation is shown in figure 2. The shape of the curve is typical of sites that are unactivated. The noise that is present in the plot is likely because the activation system was not set up to provide a low noise power supply and control lines to a probe during activation and/or CV measurement, thus the use of unshielded leads coupled outside noise into what is a very sensitive measurement. In the future, the system could be modified to provide low noise shielded leads to the probe, though it is not detrimental to the activation process at this point.

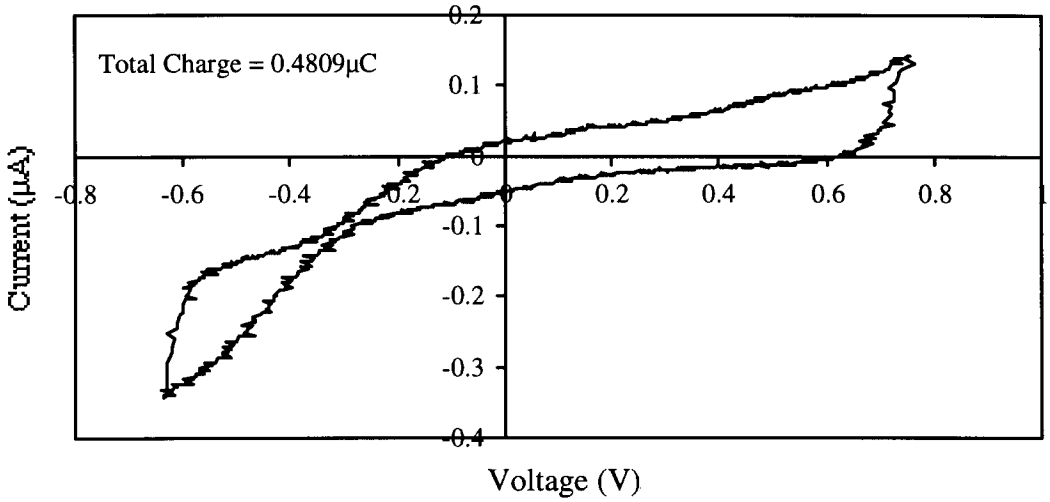

Figure 2- The CV plot of all 16 unactivated Channel A sites in parallel. The shape is typical of unactivated iridium.

Following activation, a CV plot of all 16 Channel A sites in parallel after activation is shown in figure 3. The shape of the curve is typical of activated iridium and the total charge trans-

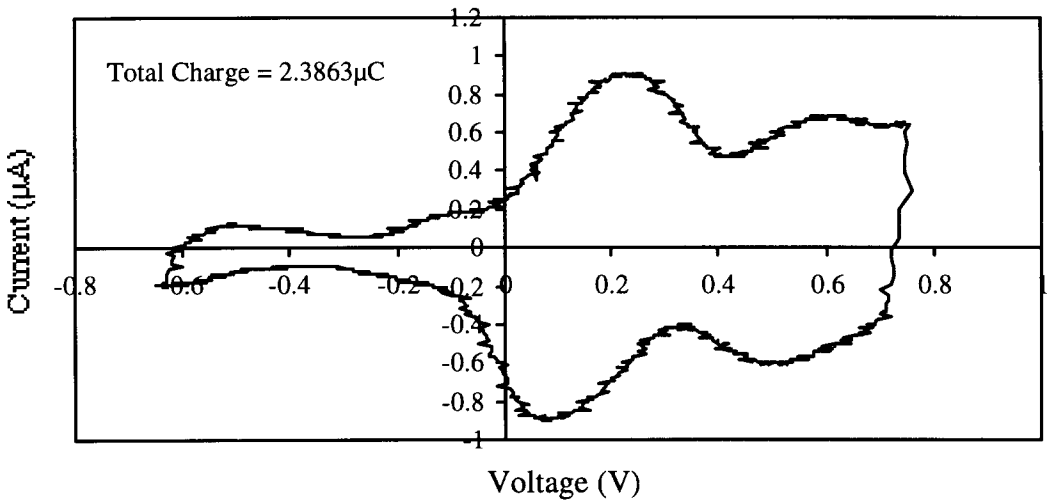

Figure 3- The CV plot of 16 activated STIM-2B sites in parallel. The shape is typical of activated iridium and the total charge transfer capability is appropriately higher.

fer capability has increased as it should have. For comparison, the CV of site A0 is shown in figure 4. The summary statistics of all of the CV measurements made on different individual sites after being activated in parallel is included in table 1. The variability between sites is quite low. Though it would be possible to match the activation levels even more closely by selecting and

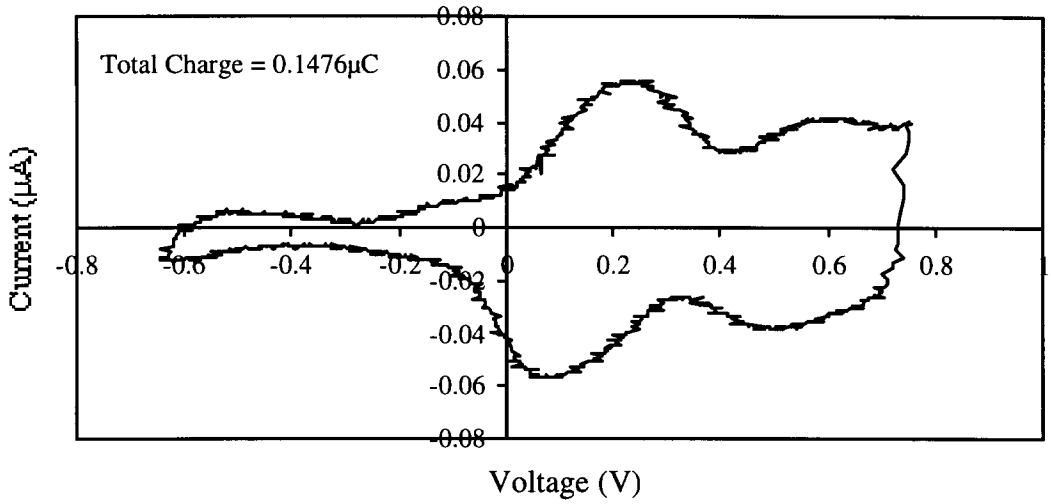

Figure 4- The CV plot of site A0 after activation. The shape is typical of an activated iridium site.

activating the sites individually, the low variability observed when the sites activated in parallel would seem to be the more viable option.

Table 1: The statistics of the charge transfer capability of individual sites after having been activated in parallel.

After 200 Pulses	
Average Charge=	0.129 mC
Variation=	.97%
After 300 Pulses	
Average Charge=	0.149 mC
Variation=	0.80%

IN-VIVO TESTING

The testing of the STIM-2Bprobe design can not be complete until the probe is actually shown to serve its intended purpose. The purpose of the STIM-2B probe is to provide a large 2D array of stimulation sites which upon insertion into neural tissue can ease the task of selectively stimulating many different points of a known grid without having to mechanically reposition the probe. In order to demonstrate this capability, a single shank, 16 site, passive recording electrode was placed in the inferior colliculus (IC) and a STIM-2B probe was placed into the dorsal cochlear nucleus (DCN) of an anesthetized guinea pig. By sequentially selecting through different sites of the 64 site array and observing the response at the recording electrode, the connection between points in the DCN and points in the IC could be observed. Figure 5 shows a histogram of 100 samples of the spontaneous single unit activity observed at a recording electrode site. Each

sample is 100mSec long. This format was used in order to compare to the spike count data as

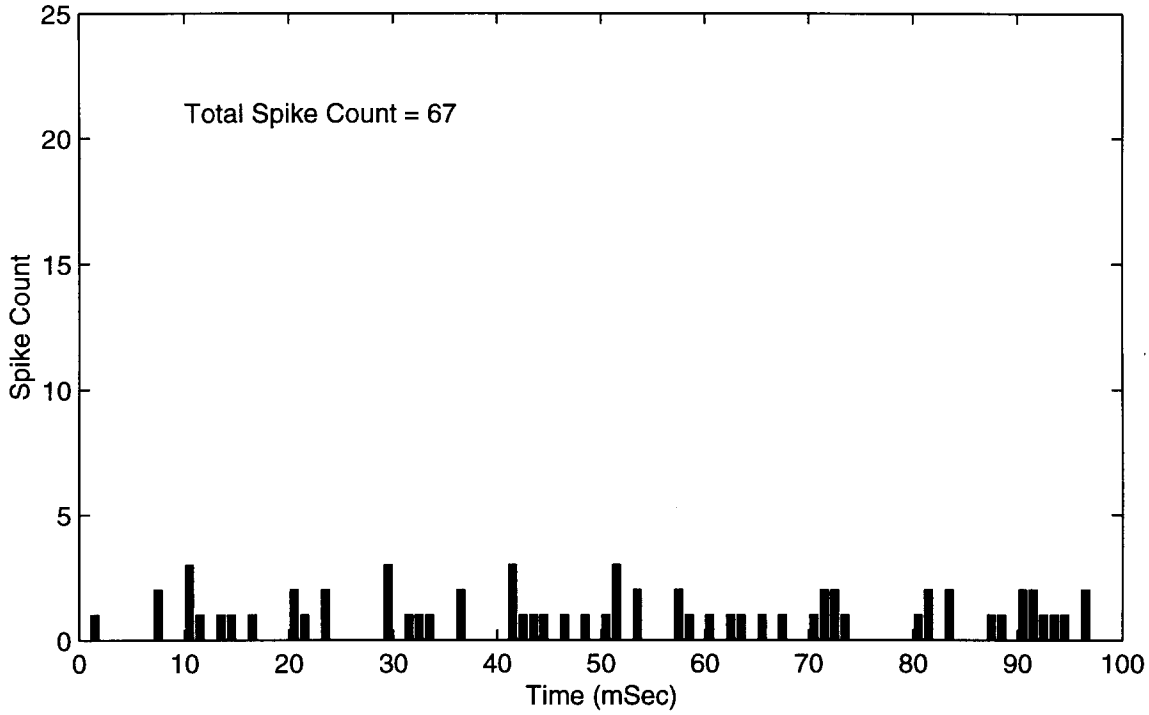

Figure 5- A histogram showing the level of the spontaneous neural activity.

related to a stimulus as will be shown later. In order to better understand the relation of different responses relating to different stimulation sites, a site map of the STIM-2B probe is shown in figure 6. Site B12 is highlighted because in the responses that were recorded and will be shown here, site B12 was found to produce the greatest response.

The stimulus used was a monopolar (referenced to a distant animal ground) 100Hz sinuosoidal burst with a duration of 50mSec. While this is not necessarily the type of stimulus that would normally be used, it was found to be quite effective in this case. When the stimulus was presented in the DCN, the response at the recording probe in the IC was simultaneously sampled (fs = 20kHz) for 100mSec. Each trial consisted of 100 presentations of the stimulus and sampled data was stored for later analysis. The analysis consisted of averaging out the stimulus artifact and the performing spike counting via spike counting routines developed by Steve Bierer. The spikes were then counted into 100 equal time bins and plotted as histograms. The total number of spikes was tabulated as well as the number of spikes the appeared while the stimulus was ON and when the stimulus was OFF, i.e. the first 50mSec and last 50mSec, respectively.

As was previously mentioned, the stimulus was cycled through the various sites until the response from site B12 was observed. A serious of responses were recorded at different levels of stimulus, two which are shown below in figures 7 & 8. Figure 7 shows the response in the IC to 12μA of stimulus current at site B12 in the DCN. Figure 7 shows the response to 100μA of stimulus current.

Another series of stimulus trials were also recorded while stimulating at a high level (97μA) from sites in close proximity to site B12. It was found that the responses were dramatically different. Keeping in mind that the stimulus level is quite large, the responses ranged from

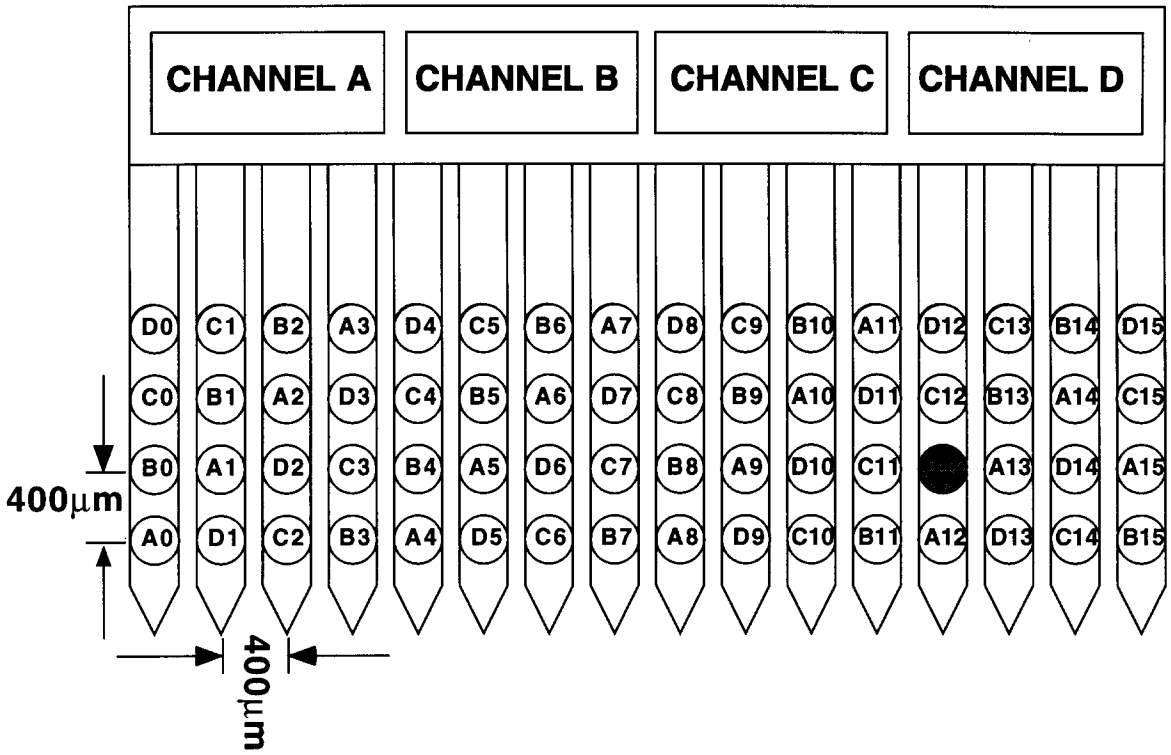

Figure 6- A site-map for the STIM-2B probe with the 'hot' site (B12) highlighted. Site B12 demonstrated some of the most significant control over the neural activity which projected to the recording site used in these examples

reduced spike counts due to stimulation at site A12 as shown in figure 9, to essentially no response due to stimulation at site C11 as seen in figure 10, to the slightly increased response of site A13 as shown in figure 11.

Yet another series of stimulus trials were recorded while stimulating at a high level (97μA) with a bipolar stimulus between site B12 and the surrounding sites. All of the surrounding sites when paired with site B12 provided a response similar the that shown in figures 12 and 13, but with varying levels of spike counts. Figure 12 is interesting because when site A12 combined with B12 as a bipolar pair, the response was significantly different than that of the site A12 monopolar stimulation as shown in figure 9 though it was similar to, but smaller than the B12 monopolar response of figure 8. Figure 13 which is the response due to the bipolar pair of B12 and D13 shows the highest response, as in the highest spike count, of any of the trials recorded. A sample sweep of an experimental trial is shown in figure 14. This data is taken from a same trial that is summarized in the histogram of figure 13.

These results are significant in that they demonstrate the capabilities of an active stimulation probe. When a large stimulating probe array is placed into neural tissue in conjunction with a recording electrode in a projecting area, experiments such a studying the mapping of the neural projections can be done easily and quickly. It is interesting to note that some of the responses were not apparent during the actual experiment, but were easily observed once the data was analyzed and the histograms were plotted.

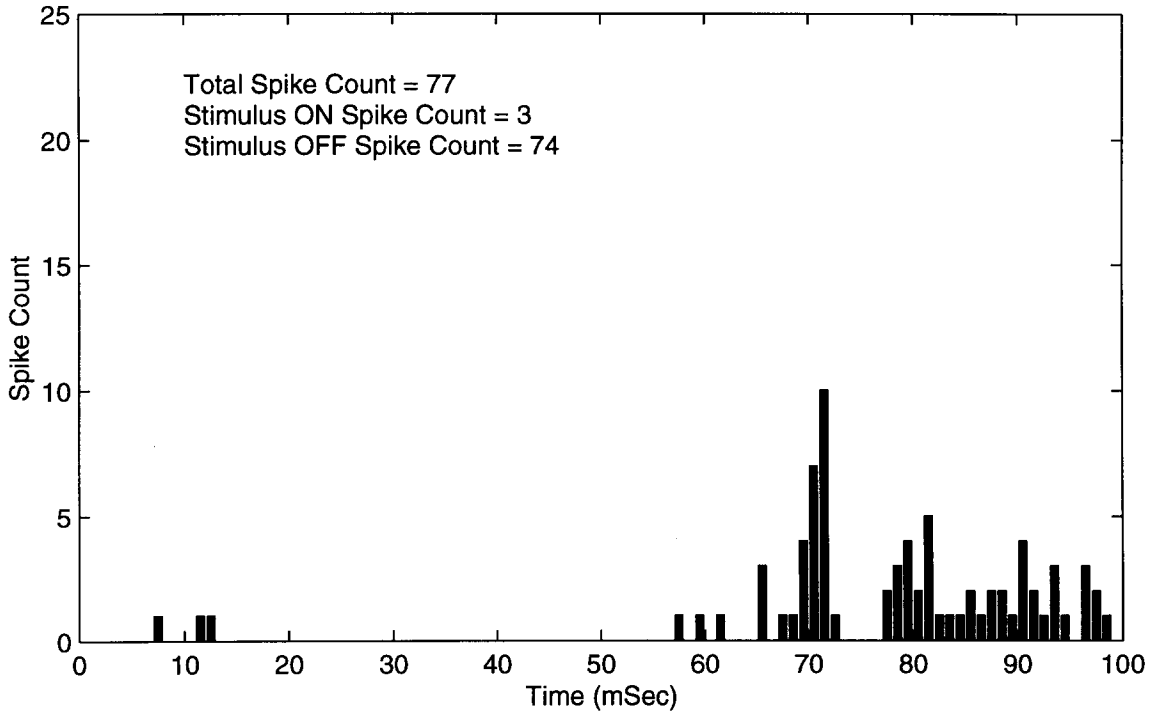

Figure 7- The response histogram with a monopolar, 12μA, 50mSec, sinusoidal-burst stimulus from site B12 (refer to the site map of fig. 6).

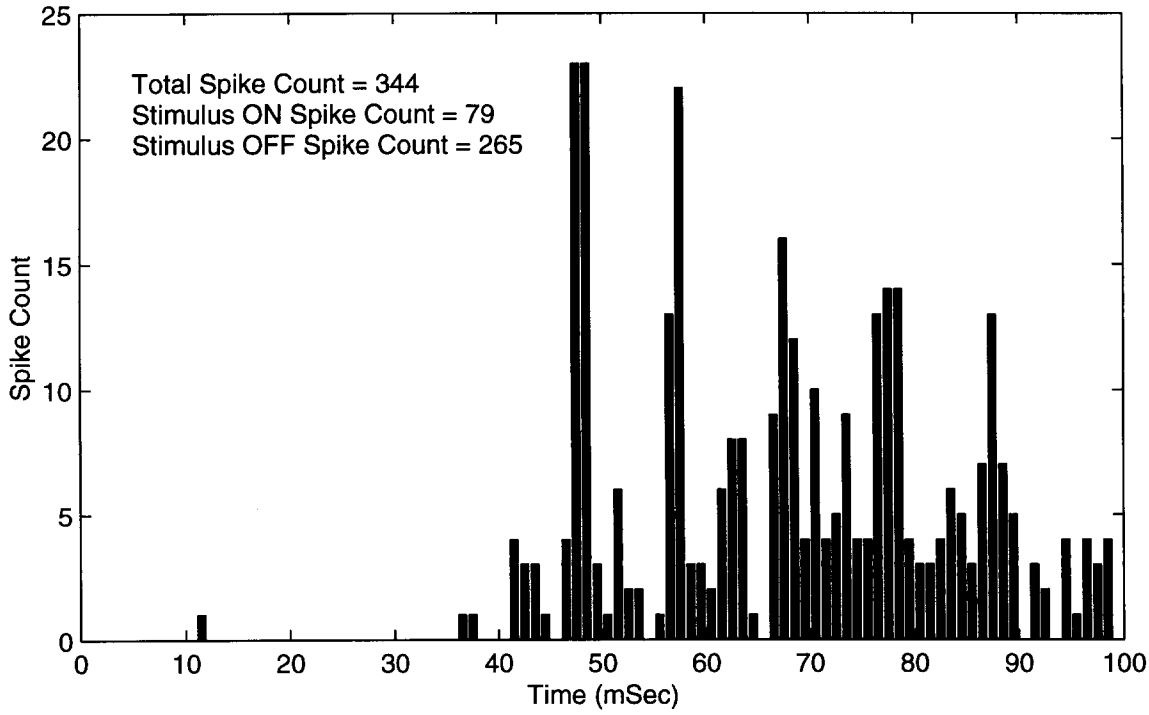

Figure 8- The response histogram with a monopolar, 97μA, 50mSec, sinusoidal-burst stimulus from site B12 (refer to the site map of fig. 6).

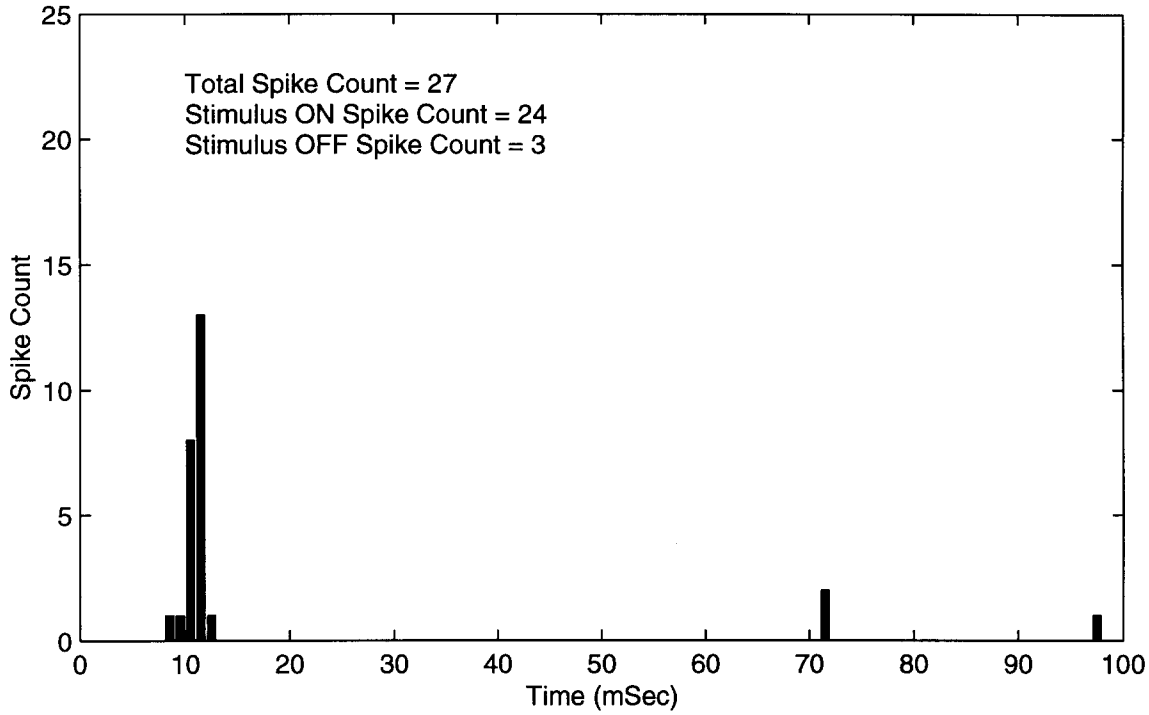

Figure 9- The response histogram with a monopolar, 97μA, 50mSec, sinusoidal-burst stimulus from site A12 (refer to the site map of fig. 6).

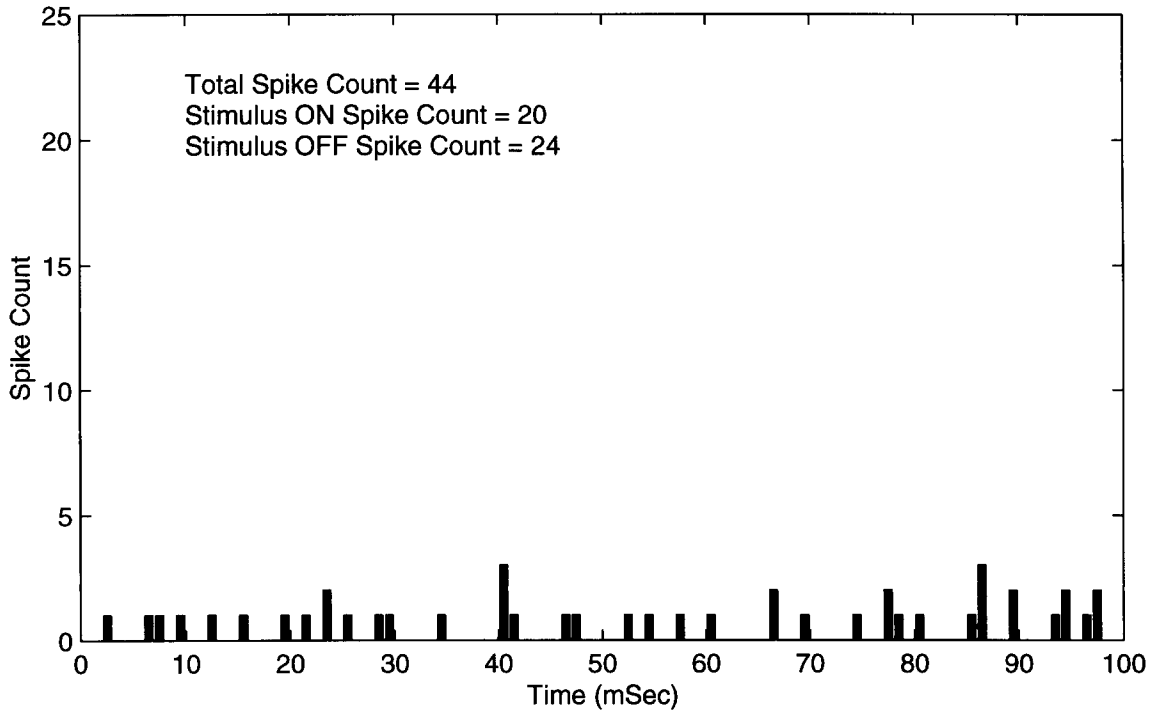

Figure 10- The response histogram with a monopolar, 97μA, 50mSec, sinusoidal-burst stimulus from site C11 (refer to the site map of fig. 6).

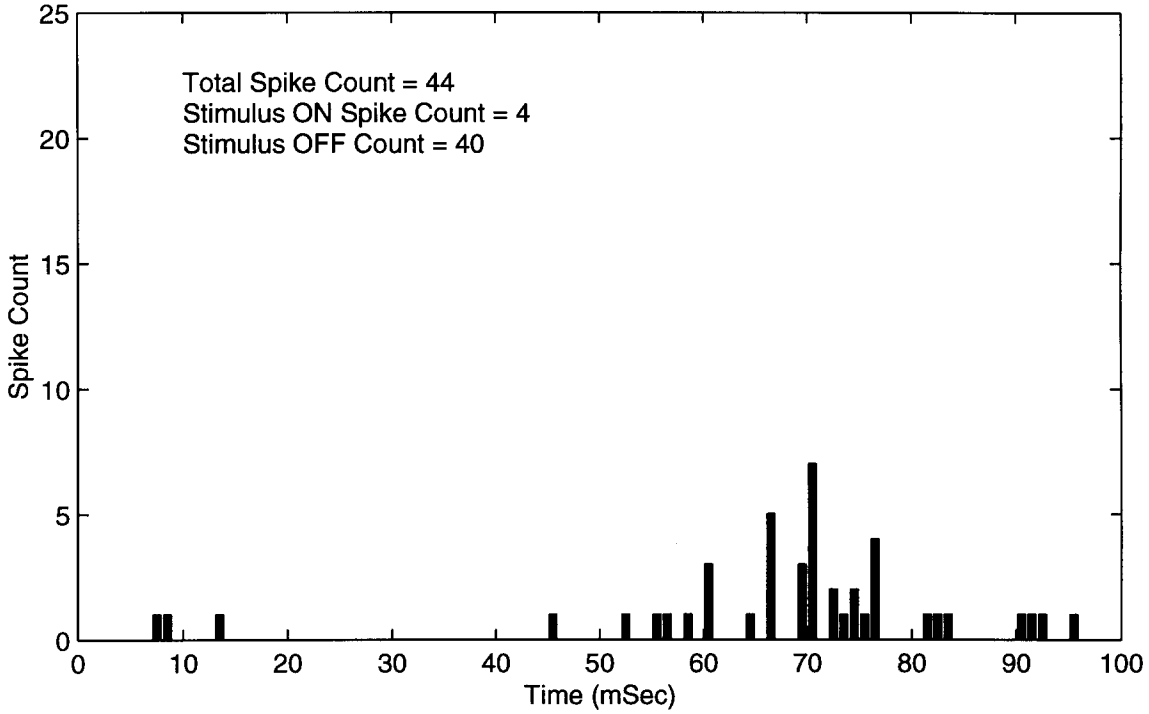

Figure 11- The response histogram with a monopolar, 97μA, 50mSec, sinusoidal-burst stimulus from site A13 (refer to the site map of fig. 6).

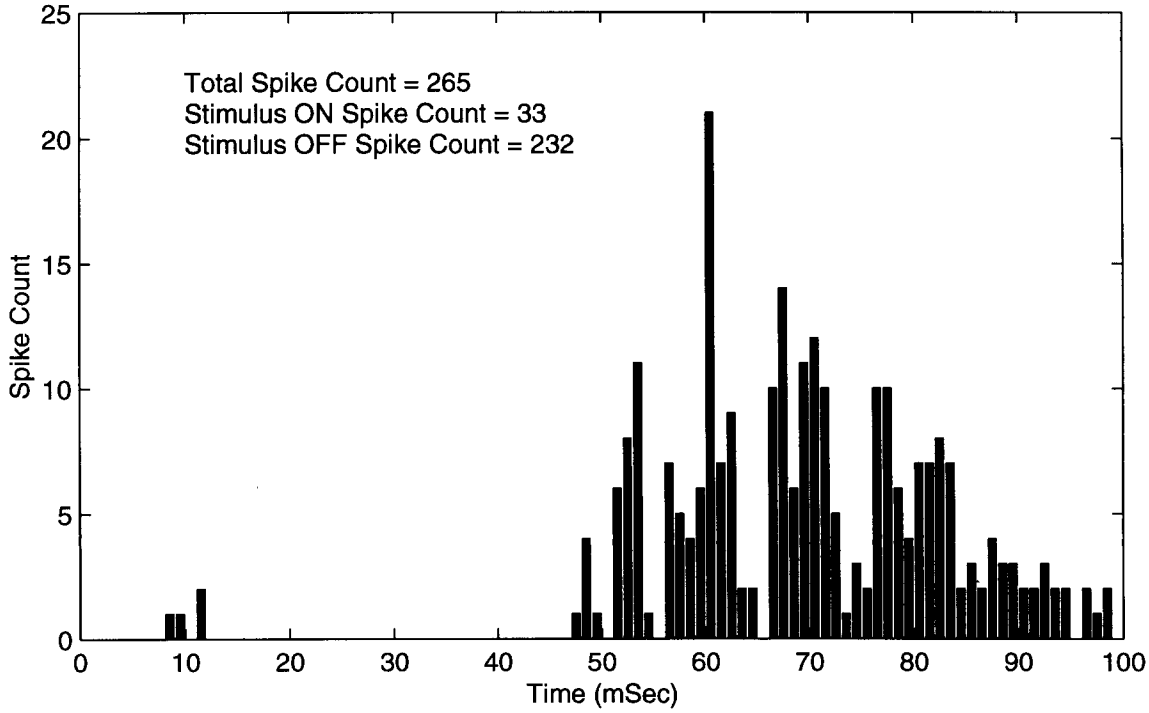

Figure 12- The response histogram with a bipolar, 97μA, 50mSec, sinusoidal-burst stimulus between the B12-A12 site pair (refer to the site map of fig. 6).

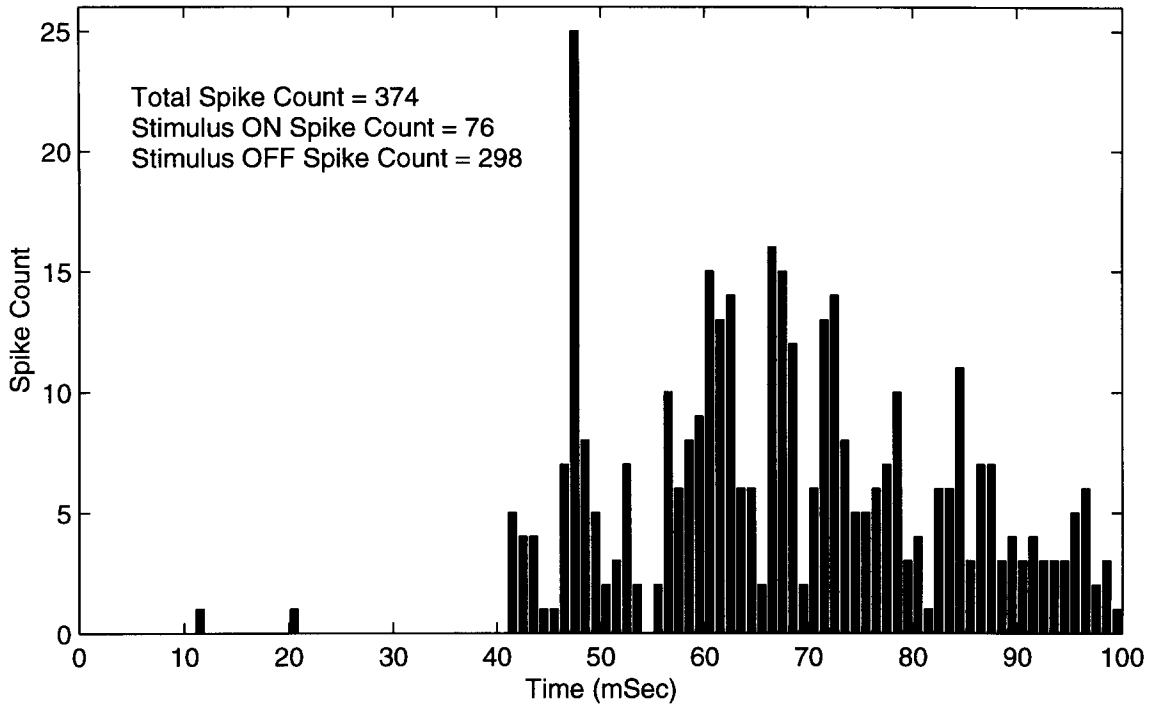

Figure 13- The response histogram with a bipolar, 97μA, 50mSec, sinusoidal-burst stimulus between the B12-D13 site pair (refer to the site map of fig. 6).

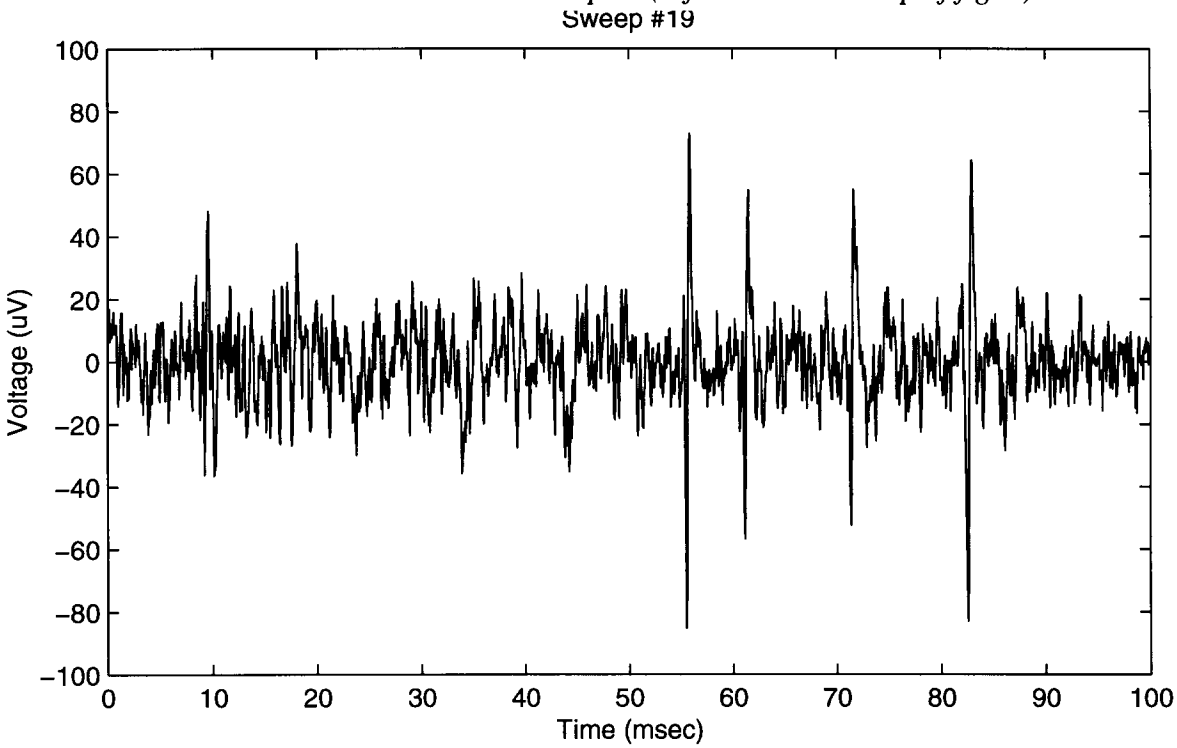

Figure 14- A sample sweep of an experimental trial. The stimulus a bipolar, 97μA, 50mSec, sinusoidal-burst stimulus between the B12-D13 site pair (refer to the site map of Fig. 6)

STIM-3B

STIM-3B is a 3-dimensional probe that is an extension of the 2-D probe, STIM-2B, and is setup to allow use as a device in chronic experiments. There are not any significant differences in probe designs, just some structural modifications to allow interconnection to a 3-D platform assembly and a few minor circuit enhancements to allow the addressing of multiple probes in a 3-D array.

As mentioned previously, the masks for the pieces of the micro-assembly, including the spacers and several different platform configurations and their integrated ribbon cables, have been made and the fabrication process is under way. The turn around time for this process is not expected to take very long because the process is nearly the same as the standard passive probe process. We plan to complete this process run and assemble some of the 3D arrays in the coming quarter. The 3D arrays are expected to provide even greater flexibility in that they will be able to access a large volume of tissue.

In summary, the STIM-2B probe has been tested in-vitro and in-vivo. The capability to perform proper activation of the Ir sites on STIM-2B was demonstrated and the measured CV curves appeared normal. The capabilities of the probe in studying the neural tissue of the CNS were demonstrated. The pieces of the STIM-3B 3D micro-assembly are being fabricated and will be completed in the coming quarter. Upon completion, the 3D arrays will be assembled and tested. We also plan to do some more testing of the STIM-2B probes in-vivo, in the coming quarter, in order to more completely characterize its performance in an experimental environment. Work on the design of the high-end 3D array, which features on-chip current generation and up to 512 or 1024 sites, is moving ahead as well.